EDITORIAL COMMENT

Quantitative PET Measurements of Myocardial Blood Flow in Young, Healthy Volunteers

What Should We Expect?*

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Sdringola et al. (1) in this issue of JACC address an issue of considerable importance, both for clinical and for research applications concerning positron emission tomography (PET) measurements of absolute myocardial blood flow (MBF). In brief, they attempted what at first blush seems a simple and obvious task; namely to define “normal” values of MBF (82Rb method) at rest and with pharmacological stress (dipyridamole) and coronary flow reserve (CFR) ratio (MBF_{dip}/MBF_{rest}). They also sought to determine the reproducibility of these measurements after a 1-week hiatus between the first and second studies and to identify what they term “unexpected” factors that may influence these measurements and their reproducibility.

The authors recruited 125 apparently healthy, asymptomatic volunteers between the ages of 20 and 40 years old for the study. Results are reported for the group as a whole as well as for 2 subgroups, apparently retrospectively defined as “true normals” and “not normals” (see Figs. 3 and 4 and Tables 1 and 2 in Sdringola et al. [1]). True normals were characterized by an absence of all of the following (Table 1 in Sdringola et al. [1]): coronary calcium on computed tomography, detectable nicotine or metabolite, detectable caffeine (>1.0 mg/ml), dyslipidemia, family history of early coronary artery disease (CAD), visual PET perfusion defect, electrocardiographic evidence of left ventricular hypertrophy, or history of hypertension. The subgroup classified as “not normal” had 1 or more of the above. The authors observed that rest MBF (0.70 ± 0.15 ml/min/g, mean ± SD) did not differ between the subgroups. However, MBF with dipyridamole and CFR were modestly but statistically greater in “true normals” versus “not normals” (respectively, 2.89 ± 0.50 vs. 2.63 ± 0.61; p < 0.005, and 4.17 ± 0.80 vs. 3.91 ± 0.86; p < 0.05). Reproducibility coefficient (Table 3 in Sdringola et al. [1]) was identical for rest MBF (35%) in the 2 subgroups and “improved,” though apparently not significantly, in “true normals” versus “not normals” for dipyridamole MBF (34% vs. 41%, respectively) and CFR (38% vs. 51%, respectively). The authors conclude “unexpected” factors noted in the previous text are present in 50% of apparently healthy young volunteers (“not normals”) and have a small but statistically significant impact, primarily on dipyridamole MBF and CFR as well as reproducibility of these parameters. Accordingly, they suggest a systematic effort should be made to identify individuals in whom 1 or more of these factors are present and to exclude them from any dataset of healthy controls (optimal age, 20 to 40 years, mixed sexes).

Although the goal of the paper is laudable and the data presented useful, there are several issues that are worth considering further. First is the broad issue of how to define “normal,” healthy controls. In the present paper, individuals from 20 to 40 years of age of either sex were recruited. Following screening, as noted previously, roughly 50% were excluded from the final dataset of true normals. The reasons for exclusion in the main, however, should not be considered unexpected. Indeed, the very purpose of screening urine for evidence of nicotine or caffeine

*Editorials published in JACC: Cardiovascular Imaging reflect the views of the authors and do not necessarily represent the views of JACC: Cardiovascular Imaging or the American College of Cardiology.

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intake, obtaining blood for lipid profile for evidence of dyslipidemia, and querying for a family history of premature CAD all reflect the well-known fact that such potential disqualifiers may be present in an apparently healthy population of younger individuals and so finding same in some of them comes as no surprise and certainly is not unexpected.

Beyond that, there is the issue of whom to include in a group of healthy controls. The authors made certain decisions, especially regarding age, sex, and lipid profile. Although 20 to 40 years of age and either sex may be appropriate for certain experimental designs, it obviously may not be for others. It is noteworthy in this regard the authors observed that women had higher rest and dipyridamole-stimulated MBF than males; an observation (i.e., higher rest MBF in women) reported by others (2). Further, use of dipyridamole at the dose employed in the present study is problematic, as the authors themselves recognize, since it may not induce maximal myocardial hyperemia and in general is less consistent and less potent in the hyperemic response it produces in comparison with that of adenosine (2,3), which is readily available and easily used. Moreover, since almost one-third of “not normals” (Table 1 in Sdringola et al. [1]) had evidence of caffeine ingestion, it is likely that much of the variation and lesser response to dipyridamole in this group compared with “true normals” (Table 3 in Sdringola et al. [1]) reflects the well-known (and expected) antagonistic effect of methylxanthines on dipyridamole-induced myocardial hyperemia.

Age, too, is known to influence rest and maximal MBF in apparently healthy individuals with low likelihood for CAD (2,4), and so both age and sex need to be taken into account when constructing a “normal” database for comparison to patients either having diagnostic quantitative PET MBF studies or those enrolled in clinical trials with quantitative PET MBF end points. It is possible race, as in the therapy of hypertension (5,6), also may play a role in terms of determining normal values for quantitative PET MBF studies. Finally, in this regard, the authors allude briefly to the fact that differences both in tracer and kinetic model employed to measure MBF may interact in ways that impact the absolute “normal” values both for rest and stress MBF. Inspection of Table 4 of their paper (1) indicates a range of “normal” rest MBF from 0.61 ± 0.09 (7) (13N-ammonia) to 1.24 ± 0.19 (8) (15 O-water) and stress MBF from 1.86 ± 0.27 (7) to 5.05 ± 0.90 (8). A recent comparison of 82 Rb with 13N-ammonia and the same tracer kinetic model indicated 82 Rb tended to overestimate rest MBF and underestimate stress (dipyridamole) MBF in comparison with 13N-ammonia (9). What all this means is that each laboratory will have to develop its own normal database using consistent technical methodology and be prepared to vary the composition of its subjects based on specifics of the study design and the hypothesis being tested. One size will not fit all.

There are several physiological points that also should be raised, and bear directly on the use of quantitative PET MBF measurements, both for clinical and research purposes. First, as the authors no doubt are aware, the notion of “normal” resting MBF itself is problematic over and above technical and epidemiological (e.g., age and sex) considerations. Efforts to correct rest MBF by indexing it to rate pressure product are crude and generally show only modest correlation between the two (2). The reasons for this are likely numerous, but two that stand out are: 1) correction for rate pressure product ignores, because it cannot be easily measured, myocardial contractility, a major determinant of MVO₂ and hence rest MBF in the normal coronary circulation (the authors allude to this in their discussion of lower resting MBF on the second visit in their “true normals” (Table 3 in Sdringola et al. [1]); and 2) heritable variation that undoubtedly plays a major role and that, in part, may reflect differences in efficiency of mitochondrial oxidative metabolism (10,11).

Further, the use of CFR to characterize the maximal dilator capacity of the coronary circulation should be discouraged for a variety of reasons. The authors’ own data indicate it is less reproducible than MBF with stress (Table 3 in Sdringola et al. [1]). Since it is a ratio, it has the potential to be quite misleading, especially if rest MBF is low. A patient with rest MBF of 0.50 ml/min/g could double or even triple that flow in response to a potent coronary vasodilator and only have maximal MBF of 1.0 to 1.5 ml/min/g, levels that fall in the normal range of rest MBF in some studies (Table 4 in Sdringola et al. [1]) and almost certainly are insufficient to deliver required levels of oxygen to myocardium under conditions of maximal exercise stress (12). Yet CFR of 2× to 3× is commonly considered “normal” (13) and would fall within 2 SD of the mean reported in the current study (4.03 ± 0.85) (Table 4 in Sdringola et al. [1]). Moreover, it has been shown that a single measurement of adenosine-stimulated maximal myo-
Cardiac blood flow provides excellent discrimination between coronary vessels with >70% stenosis and those with lesser or no stenosis (14). Accordingly, there is little to be gained by measuring rest MBF for purposes of computing CFR if the objective of the endeavor is to diagnose CAD or assess the response to an intervention designed to increase maximal MBF.

In summary, therefore, the paper by Sdringola et al. (1) demonstrates the need for meticulous attention to detail both in documenting the clinical status of subjects to be included in a normal database for quantitative PET measurements of MBF and in the requirement for thoughtful consideration of who those subjects should be. As with most well-done papers, it also raises a number of issues, noted in the previous text, worthy of additional consideration and future research.

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Key Words: healthy controls myocardial blood flow PET quantitative.